

Food and Drug Administration Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Misty M. D'Ottavio, Senior Manager Regulatory Affairs Merz Pharmaceuticals, LLC 4215 Tudor Lane Greensboro, NC 27410

RE: NDA #019599

Naftin® (naftifine hydrochloride) Cream, 2% MA #109

Dear Ms. D'Ottavio:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed Merz Pharmaceuticals, LLC (Merz) webpages for Naftin® (naftifine hydrochloride) Cream, 2% (Naftin Cream, 2%) titled, "Naftin Home," "Physician Information: Twice as Strong, Half as Long," "Physician Information: Clinical Efficacy in Tinea Cruris," and "Physician Information: Clinical Efficacy in Tinea Pedis," as well as two online banners for Naftin Cream, 2%, submitted under cover of Form FDA 2253. These promotional materials are misleading because they omit and minimize important risk information. In addition, these materials include unsubstantiated efficacy claims, unsubstantiated superiority claims, claims that overstate the product's efficacy, and other misleading claims about the drug. Thus, the webpages and banners misbrand Naftin Cream, 2% in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a), (n); 321(n). See 21 CFR 202.1(e)(5); (e)(6)(i), (ii); (e)(7)(i).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Naftin Cream, 2%.²

According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI):

NAFTIN (naftifine hydrochloride) Cream, 2% is indicated for the treatment of: interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton rubrum* in adult patients ≥18 years of age.

The PI contains a Warning and Precaution regarding the local adverse reactions.

Reference ID: 3350378

¹ Available at http://www.naftin.com (Last accessed July 31, 2013).

² This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece(s) cited in this letter.

Specifically, if irritation or sensitivity develops with Naftin Cream 2%, treatment should be discontinued. The most common adverse reaction associated with Naftin Cream, 2% is pruritus.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The banners include the indication for Naftin Cream, 2%, and several other efficacy claims, including "Twice as Strong Half as Long," and "Once a day for 2 weeks." However, the banners fail to include **any** risk information associated with the drug. We note the banners present the statement, "Visit www.NAFTIN.com for full Prescribing Information" at the bottom of each banner. However, this does not mitigate the misleading omission of risk information from the banners. In addition, while each webpage discloses the common adverse reaction pruritus under the statement "**Important Safety Information**" (emphasis original), they completely omit the warning and precaution for local adverse reactions associated with Naftin use. By failing to include important risks associated with Naftin Cream, 2%, the banners and webpages misleadingly suggest that Naftin Cream, 2% is safer than has been demonstrated.

The "Physician Information: Twice as Strong, Half as Long" webpage makes the claim, "Proven safety established from naftifine hydrochloride for over 20 years." This claim misleadingly minimizes the risks associated with Naftin Cream, 2% because it implies that Naftin Cream, 2% has a longer record of safety than has been demonstrated. We acknowledge that a formulation containing naftifine hydrochloride was initially approved in 1988. We also acknowledge that naftifine hydrochloride is the active ingredient in the promoted product, Naftin Cream, 2%. However, the Naftin Cream, 2% formulation of naftifine hydrochloride constitutes a different strength and dosage approved in 2012 that does not have a safety profile established based on a 20 year history of use. Thus, this claim implies that Naftin Cream, 2% is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Unsubstantiated Efficacy Claims

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience.

The "Physician Information: Clinical Efficacy in Tinea Cruris" webpage and "Physician Information: Clinical Efficacy in Tinea Pedis" webpage contain the following claims:

"8X greater clinical success vs vehicle at Week 4, NAFTIN Cream 2% (84%) vs

- vehicle (10%), (P<0.001, n=146)^{[3]§}" [Physician Information: Clinical Efficacy in Tinea Cruris webpage]
- "2X greater clinical success vs vehicle at Week 6, NAFTIN Cream 2% (78%) vs vehicle (49%), (two sided P<0.001, n=217)^{[4]§}" [Physician Information: Clinical Efficacy in Tinea Pedis webpage]

"§ Clinical Success is defined as absence or near absence of erythema, pruritus, and scaling (score of 0 or 1 on a 4-point scale)."

These claims are misleading because they are not supported by substantial evidence or substantial clinical experience. The references cited to support these claims describe the clinical studies associated with the approval of Naftin Cream, 2%. The primary endpoint of the clinical studies evaluating Naftin Cream, 2% in the treatment of tinea cruris and tinea pedis was the composite endpoint of complete cure, which was defined as both clinical cure (absence of erythema, pruritus, and scaling) and mycological cure (negative KOH preparation and dermatophyte culture). While an endpoint termed "clinical success" was described in the clinical study protocol, it was not controlled for multiplicity. In addition, the absence or near absence of erythema, pruritus, and scaling alone (i.e., "clinical success") does not represent a clinically meaningful endpoint as it may represent mere symptomatic improvement rather than demonstrating a mycological effect of the active ingredient. Therefore, any claims of efficacy suggesting "clinical success" as defined above are not supported by substantial evidence or substantial clinical experience and are misleading.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience.

The banners and the "Naftin Home" webpage include the following claims:

- "Twice as Strong Half as Long . . . Once a day for 2 weeks" [Banners]
- "Twice as Strong Half as Long" ["Naftin Home" webpage]

These claims misleadingly suggest that Naftin Cream, 2% is superior to other anti-fungal treatments based on efficacy and dosing schedule, when this is not supported by substantial evidence or substantial clinical experience. We are not aware of any adequate, well-controlled head-to-head studies demonstrating that Naftin Cream, 2% offers superior efficacy when compared to other anti-fungal treatment options. In addition, while we acknowledge that Naftin Cream, 2% has a suggested 2-week treatment length, there are other prescription products currently available that are FDA-approved for interdigital tinea pedis, tinea cruris,

Reference ID: 3350378

³ Parish LC, Parish JL, Routh HB, et al. A double-blind, randomized, vehicle-controlled study evaluating the efficacy and safety of naftifine 2% cream in tinea cruris. *J Drugs Dermatol.* 2011; 10 (10): 1142-1147.

⁴ Parish LC, Parish JL, Routh HB, et al. A double-blind, randomized, vehicle-controlled study evaluating the efficacy and safety of naftifine 2% cream in tinea pedis. *J Drugs Dermatol.* 2011; 10 (11): 1282-1288.

and tinea corporis and have a recommended treatment length of 2-weeks or less. Therefore, the suggestion that Naftin Cream, 2% is superior to other anti-fungal products is not supported by substantial evidence or substantial clinical experience.

Overstatement of Efficacy

The "Physician Information: Twice as Strong, Half as Long" webpage includes the claim, "Improvement in results **continues** 2-4 weeks after treatment" (emphasis added). This claim is misleading because it implies that Naftin Cream, 2% is effective prior to week 4 (2 weeks post treatment) in the treatment of tinea cruris and prior to week 6 (4 weeks post treatment) in the treatment of tinea pedis when this has not been demonstrated by substantial evidence or substantial clinical experience. The primary endpoint in Naftin Cream, 2% clinical studies for tinea cruris and tinea pedis was complete cure at **week 4** and **week 6**, respectively. While patients were also evaluated at week 2 in the tinea cruris study and weeks 2 and 4 in the tinea pedis study, these earlier time points were not prespecified endpoints for use in support of efficacy claims. Therefore, the suggestion that efficacy with Naftin Cream, 2% can be expected prior to week 4 and week 6 for tinea cruris and tinea pedis is not supported by substantial evidence or substantial clinical experience.

Misleading Claim

The "Physician Information: Twice as Strong, Half as Long" webpage makes the following claim (emphasis in original):

"More than **90%** of patients were able to adhere to the full course of treatment" [2,3]

This claim is misleading because it suggests that a very high percentage of patients will adhere to the full course of Naftin Cream, 2% therapy, in the absence of substantial evidence or substantial clinical experience. As with the claims cited earlier in this letter, the references cited to support these claims describe the clinical studies associated with the approval of Naftin Cream, 2%. While these studies evaluated the safety and efficacy of Naftin Cream, 2% in treating tinea cruris and tinea pedis, they did not include prespecified primary or secondary endpoints designed to evaluate the claimed outcome of patient adherence. In addition, while the study included results from patient diaries that were used to evaluate adherence to treatment, there is no documentation to support that the diaries utilized in the studies are well-defined and reliable assessments of patient adherence for use in support of efficacy claims. Consequently, these studies do not constitute substantial evidence to support that the patient responses in the diaries are valid or reliable. Therefore, suggestions that a high percentage of patients will adhere to the full course of Naftin Cream, 2% therapy are misleading in the absence of substantial evidence or substantial clinical experience.

Conclusion and Requested Action

For the reasons discussed above, the banners and webpages misbrand Naftin Cream, 2% in violation of the Act, 21 U.S.C. 352(a), (n); 321(n). See 21 CFR 202.1(e)(5); (e)(6)(i), (ii); (e)(7)(i).

OPDP requests that Merz immediately cease the dissemination of violative promotional materials for Naftin Cream, 2% such as those described above. Please submit a written response to this letter on or before August 14, 2013 stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Naftin Cream, 2% that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266 or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA #109 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Naftin Cream, 2% comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Susannah K. O'Donnell, MPH Regulatory Review Officer Office of Prescription Drug Promotion

{See appended electronic signature page}

Michael Sauers, MPP Acting Division Director Office of Prescription Drug Promotion This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature. /s/ SUSANNAH O'DONNELL 07/31/2013 MICHAEL A SAUERS

07/31/2013